BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAW (BRONJ)

BISPHOSPHONATES AND WHAT HAPPENS TO BONE

- VINCENT E. DIFABIO, DDS, MS
  MEMBER OF THE COMMITTEE ON HEALTHCARE AND ADVOCACY FROM THE AMERICAN ASSOCIATION OF ORAL & MAXILLOFACIAL SURGERY (AAOMS)
  ASSOCIATE PROFESSOR OF ORAL & MAXILLOFACIAL SURGERY UNIVERSITY OF MARYLAND, BALTIMORE, MARYLAND
  AND PRIVATE PRACTICE OF ORAL & MAXILLOFACIAL SURGERY, FREDERICK, MARYLAND

BISPHOSPHONATES AND WHAT HAPPENS TO BONE

- PRESENT THE POTENTIAL FOR A DIFFERENT ETIOLOGY OF BONE DESTRUCTION IN THE MAXILLA AND MANDIBLE AND
- THE NEED FOR SPECIFIC CODES TO REPRESENT THIS DIFFERENT ETIOLOGY OF BONE DESTRUCTION SEEN IN THE MAXILLA AND MANDIBLE

OSTEONECROSIS OF THE JAW

- NOT A NEW DISEASE OR PHENOMENON
- “PHOSSY JAW” DATES BACK TO THE 19TH CENTURY
- RELATED TO MATCHSTICK MAKING
- HIGH LEVELS OF PHOSPHORUS

BISPHOSPHONATES

- ARE USED TO TREAT SEVERAL DISEASE ENTITIES
- OSTEOPOROSIS
- CANCER PATIENTS
- RECENT PAPERS HAVE SHOWN THAT A JAW OSTEONECROSIS OF ASEPTIC ETIOLOGY IS ASSOCIATED WITH THE USE OF BISPHOSPHONATES

OSTEOPOROSIS

- TREATED WITH BISPHOSPHONATES (BPs)
- MANY PEOPLE WORLD WIDE ARE RECEIVING THESE TYPES OF MEDICATIONS
- IS THIS TREATMENT OF OSTEOPOROSIS WITH BPs OF CONCERN???

Osteoporosis

- **Primary disease**: ⇩ quantities of sex hormones
  - Phase 1: trabecular bone resorption due to estrogen deficiency. Peaks after 4-8 years (women only)
  - Phase 2: persistent, slower loss of both trabecular and cortical bone which is mainly due to decreased bone formation (men and women)

Osteoporosis

- **Secondary disease**: consequence of other diseases or medications
  - Long term steroid use, Cushing's disease, anorexia nervosa, athletic amenorrhea, HPT, cystic fibrosis, inflammatory bowel disease, rheumatoid arthritis
- Observed in young/old, men/women
- Osteoporosis ICD-9-CM Codes: 733.0 – 733.09

Osteoporosis

- Unbalanced bone remodeling where

  bone formation ≠ bone resorption
- Defined as a disease with low bone mass and deterioration of bone structure resulting in bone fragility and increase risk of fracture
- Females >>>Males
- Primary *vs*. Secondary

Lerner AH, J. Dent Res 85. 2006

Osteoporosis is a BIG problem in the USA!

Surgeon General Report (2004)

- 40% of American women > 50 yo. Will experience an osteoporotic fracture
- 13% of men 50 yo.
- By 2020 it is estimated that 50% of all Americans over the age of 50 will be at risk of developing osteoporosis
- Direct cost expenditures for 1.3 million fx per yr = $14 billion +

OSTEOPOROSIS

- THE BIG QUESTION IS WILL THESE PATIENTS IN THE FUTURE DEVELOP A SIMILAR OSTEONECROSIS OF THE JAW???

OSTEORADIONECROSIS

- NOTED WITH THE INTRODUCTION OF RADIATION THERAPY TO TUMORS OF THE HEAD AND NECK
- RADIATION CREATES HARD AND SOFT TISSUE HYPOXIA, HYPO-CELLULARITY AND HYPO-VASCULARITY
- RESULTS IN A SIGNIFICANT DECREASE IN HEALING AND NECROSIS OF BONE
- OSTEORADIONECROSIS OF THE JAWS
  ICD - 9- CM CODE: 526.89

OSTEOMYELITIS

- BACTERIAL INFECTION OF THE BONE
- PRIMARY OR SECONDARY TO DENTAL OR OTHER ORAL INFECTIONS
- OSTEOMYELITIS OF THE BONE: 730 – 730.9 INCLUDES ACUTE AND CHRONIC and
- OSTEOMYELITIS OF THE JAW: 526.4 and 526.5

PATHOPHYSIOLOGY

- ALTHOUGH THE OSTEORADIONECROSIS (RADIATION INDUCED), OSTEOMYELITIS (BACTERIAL INFECTION) AND BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAW (ASEPTIC NECROSIS & DRUG INDUCED) ARE DIFFERENT IN ETIOLOGY, THEY ARE SIMILAR IN PATHOLOGY AND SECONDARY INFECTIONS
- AND WILL THE OSTEOPOROSIS PATIENTS TREATED WITH BPs DEVELOP A SIMILAR ONJ IN THE FUTURE??

ICD-9-CM

- WE HAVE SPECIFIC ICD-9-CM CODES FOR OSTEOPOROSIS, OSTEOMYELITIS AND OSTEORADIONECROSIS
- SO WHY NOT USE THESE CODES FOR BP RELATED ASEPTIC OSTEONECROSIS OF THE JAW OR BRON JAW??

NEED FOR A SPECIFIC CODE

- REPORTING INCIDENCE OF OCCURRENCE AND TRACKING
- RESEARCH
- EVALUATION & MANAGEMENT AND SURGICAL PROCEDURES OF MAXILLA AND MANDIBLE LINKED TO A SPECIFIC VS NON-SPECIFIC ICD-9CM CODE

BISPHOSPHONATE RELATED OSTEONECROSIS OF THE JAW (ONJ)

- FIRST RECOGNIZED IN 2003 AS A COMPLICATION OF BISPHOSPHONATE THERAPY
- HIGHER FREQUENCY IN THE MANDIBLE (63%) THAN IN THE MAXILLA (38%)
- ETIOLOGY IS UNCLEAR AND IS THE SUBJECT OF CURRENT RESEARCH AND INVESTIGATION

BRONJ

- CAN BE RELATED TO DENTAL TREATMENT
- CAN BE RELATED TO DENTAL PATHOLOGY
- CAN BE SPONTANEOUS WITH DENTAL ETIOLOGY
- CAN BE RELATED TO DENTURE IRRITATION OR WEAR
- CAN BE UNRELATED TO ANY OF THE ABOVE
- CAN BE RELATED TO LOCAL TRAUMA
- CAN BE UNKNOWN IN ETIOLOGY

PROPOSED INDUCTION MECHANISMS

- INHIBITION OF OSTEOCLAST ACTIVITY
- REDUCES BONE TURNOVER
- REDUCING REMODELING
- DECREASED NEW BONE FORMATION
- ETIOLOGY IS UNKNOWN
- BUT IS LIKELY MULTIFACTORIAL

BRONJ

- TRUE INCIDENCE IS DIFFICULT TO ESTIMATE
- DEPENDING ON RECENT RETROSPECTIVE REPORTS COULD BE <1%-9% OF CANCER PATIENTS RECEIVING BISPHOSPHONATES
- SEEN IN CANCER PATIENTS WITH MULTIPLE ANTINEOPLASTIC MEDICATIONS AS WELL AS BISPHOSPHONATES
- MULTIPLE MYELOMA, BREAST CANCER AND PROSTATE CANCER ARE THE PRIMARY NEOPLASMS AFFECTED
- AND WHAT ABOUT OSTEOPOROSIS PATIENTS TREATED WITH BPs?????

ONJ

- MULTIPLE PAPERS RELATING BPs WITH ONJ SINCE 2003
- RELATED TO METHOD OF ADMINISTRATION OF BPs: IV VS PO
- RELATED TO THE DURATION OF ADMINISTRATION
- VERY SERIOUS SEQUELAE WHEN ONJ DEVELOPS

BP's Mechanism of action

1) Tissue level

a. reduction of bone turnover

2) Cellular level

a. inhibition of osteoclastic activity on the bone surface (Rodan et al., Strewler)

b. inhibition of osteoclast recruitment on the bone surface (Rodan et al., Vitte et al.)

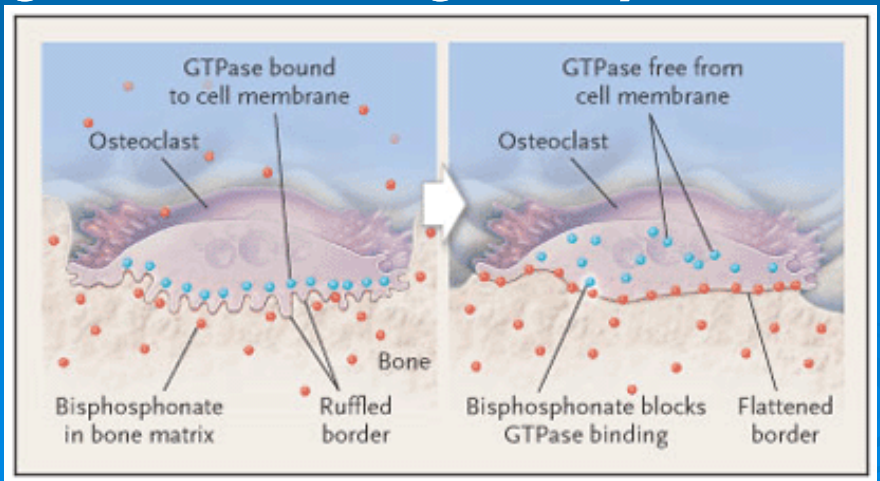
c. osteoclast apoptosis (Hughes et al., Rogers et al.)

BP's Mechanism of action

3) Molecular level

Interferes with osteoclast intercellular biochemical pathways

- **Inhibition of farnesyl diphosphate synthase**
- **Metabolized to toxic analogue of ATP (non-nitrogen containing BP's)**



Strewler GJ. N Engl J Med 2004;350:1174

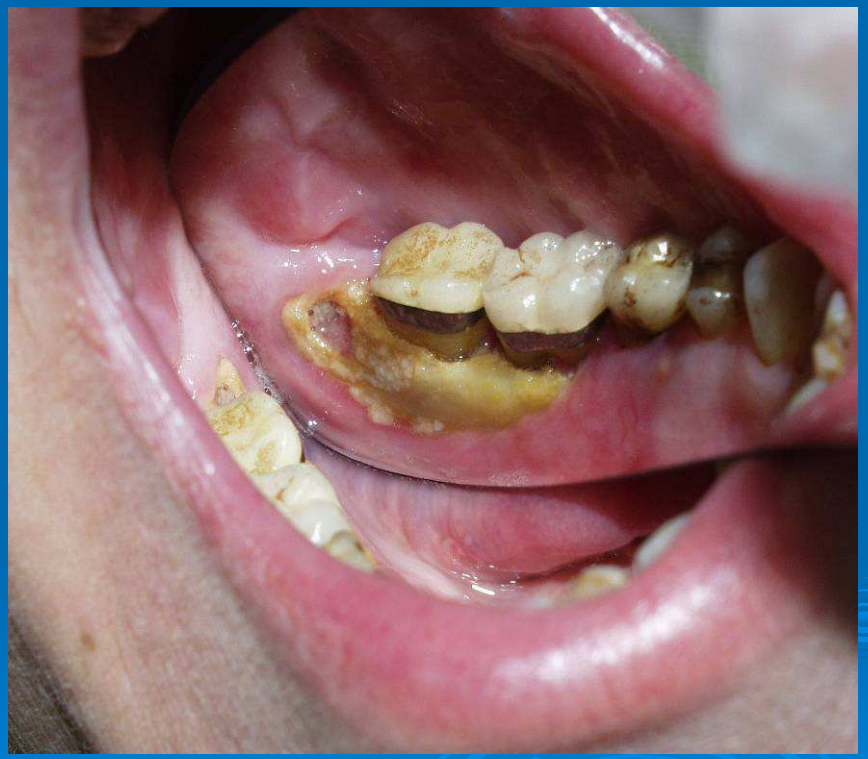
Bisphosphonates

- **Pharmacologic action:**
  - Inhibition of bone resorption
- **Pharmacokinetics:**
  - **Distribution**: Rapid accumulation in sites of increased bone deposition/resorption, low plasma levels, ***½ life of "years"***
  - **Metabolism**: Not metabolized (nitrogen containing)
  - **Excretion**: Renal

Staging

Stage 1

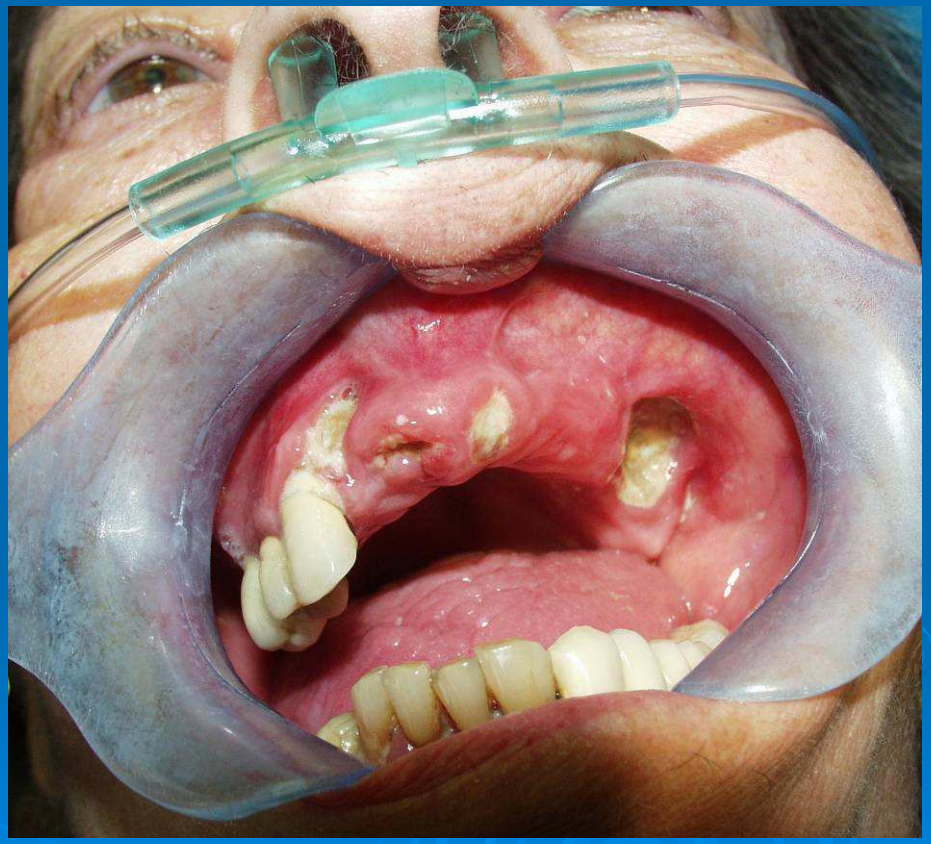
- Characterized by exposed bone that is asymptomatic with no evidence of significant soft tissue infection



Staging

Stage 2

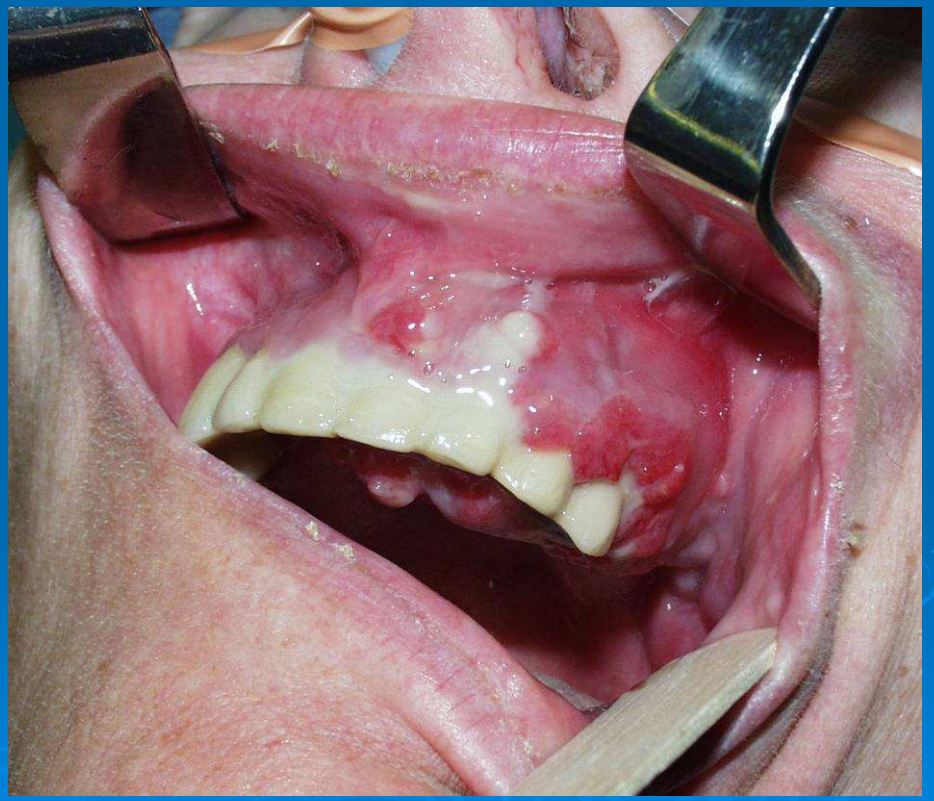
- Exposed bone associated with pain, soft tissue and/or bone infection



Staging

Stage 3

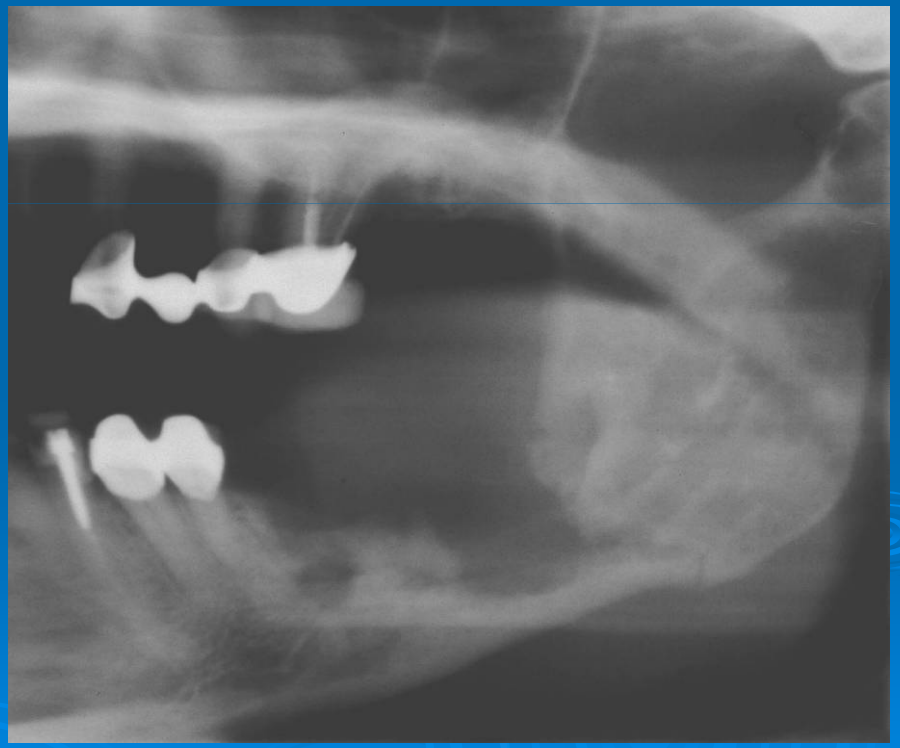
- Pathologic fracture
- Exposed bone associated with soft tissue infection or pain that is not manageable with antibiotics due to the large volume of necrotic bone.



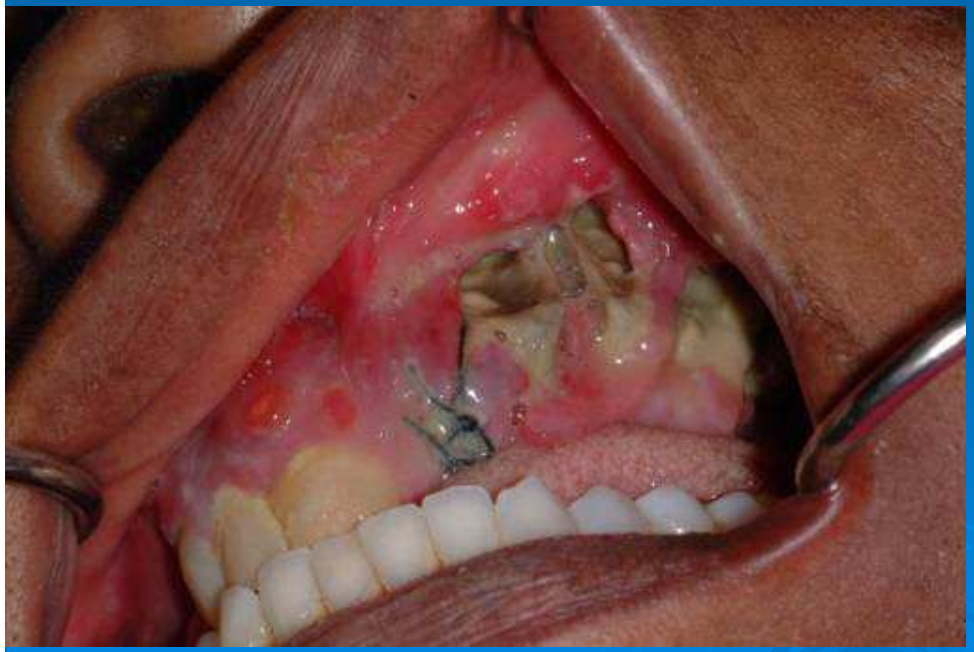
Staging

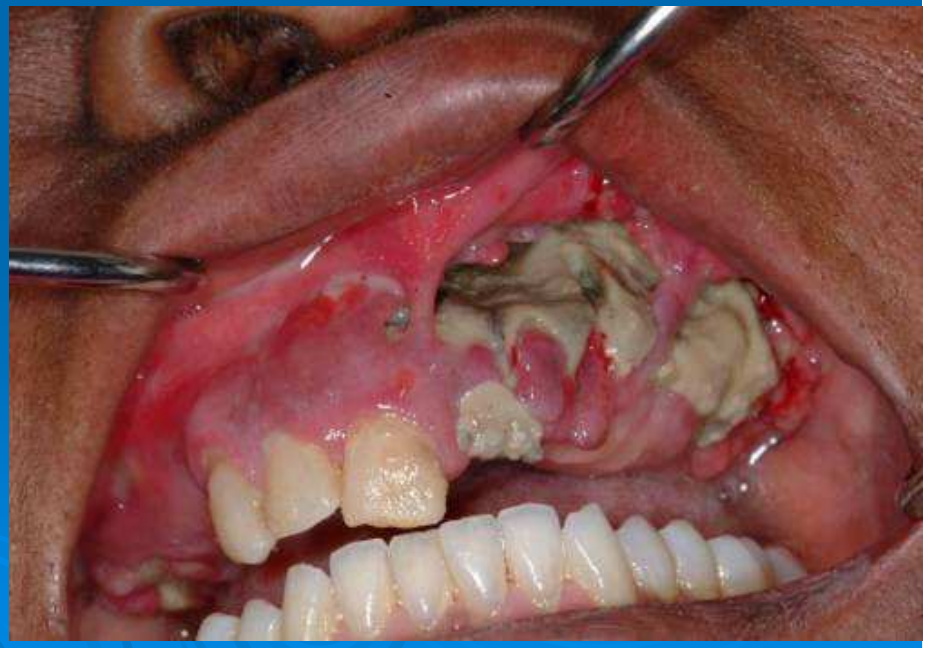
Stage 3

- Pathologic fracture
- Exposed bone associated with soft tissue infection or pain that is not manageable with antibiotics due to the large volume of necrotic bone.



A 40 yo with female with a diagnosis of breast cancer and Zometa therapy (6 months) presents with pain, exposed and infected maxillary bone following extraction





Relative Potency

Etidronate (Didronel)	1
Tiludronate (Skelide)	10
Pamidronate (Aredia)	100
Alendronate (Fosamax)	1,000
Risedronate (Actonel)	10,000
Ibandronate (Boniva)	10,000
Zolendronic acid (Zometa)	>100,000

PROPOSAL

- NEW DIAGNOSTIC ICD-9CM CODE FOR THE ASEPTIC NECROSIS OF BONE IN THE JAWS:
- NEW CODE: 733.45 JAW (MAXILLA AND MANDIBLE) AND
- APPROPRIATE NEW E CODES TO IDENTIFY THE SPECIFIC ROUTE OF ADMINISTRATION
- E933.6 ORAL BISPHOSPHONATES
  AND
  E933.7 INTRAVENOUS BISPHOSPHONATES

Combinations

- Use E933.1 antineoplastic & immunosuppressive drugs and
- May also need to Code for the primary neoplasm (most common ones are prostate, breast and myeloma)